Synthesis and Biological Evaluation of 4-Chloro-3,5-dinitrobenzotrifluoride Analogues as Antileishmanial Agents

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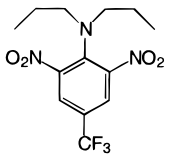
Desnitro analogues of 4-chloro-3,5-dinitrobenzotrifluoride (chloralin) (**2**), an in vitro microtubule inhibitor of several *Leishmania* species, have been synthesized from 2-halo-5-(trifluoromethyl)-benzenesulfonyl chlorides **4** and **5**. The analogues exhibited moderate to excellent activity when tested against *Leishmania donovani* amastigotes in vitro. Two representative compounds, **7f** and **8**, were tested against the Khartoum strain of *L. donovani* in a hamster model using chloralin (**2**) and Glucantime (one of the current therapeutics of choice in the treatment of *Leishmania*) as standards, the results of which will be discussed herein.

Introduction

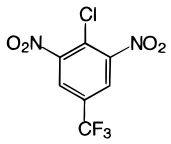
Leishmaniasis is a parasitic infection transmitted to humans by the female phlebotomus sandfly. This disease is endemic to both the tropical and subtropical regions of Africa, Asia, the Mediterranean, Southern Europe, and both Central and South Americas. The clinical manifestations of this disease vary widely and are categorized by symptoms such as lesions on the face, arms, legs (cutaneous, diffuse cutaneous, disabling), and mucous membranes of the nose and mouth (mucocutaneous, mutilating). The parasite can also invade the spleen, liver, bone marrow, lymph nodes, and skin (visceral, kala azar, fatal). The severity of the disease is determined by factors such as host immunity, parasite virulence, and host or vector behavior. It has been estimated that 12 million people are infected with leishmaniasis and that 350 million people are at risk in about 88 countries. There are approximately 2 million new cases of leishmaniasis per year, of which only 600 000 are officially reported. Hospitalization is necessary for treatment to occur.[1]

The current chemotherapeutic treatments of choice for leishmaniasis are two pentavalent antimony compounds: sodium stibogluconate (Pentostam) and meglumine antimoniate (Glucantime).[2] They are rapidly excreted from the kidneys with virtually no accumulation in the body. However, they have serious side effects associated with them including nausea, diarrhea, convulsions,[3] and even cardiotoxicity.[4] Antimony-resistant strains have also been reported.[5] Secondary treatment agents include pentamidine and amphotericin B, which also have serious side effects associated with them.[3] Because of the adverse side effects of these treatment regimes, much attention has been focused on the discovery and development of new and less toxic chemotherapeutic agents.

This effort has produced many novel and interesting treatments such as liquid nitrogen therapy[6] and the utilization of localized current field-radio frequencies.[7] The more traditional approach of generating synthetic analogues of existing drugs has led to the investigation of dinitroanilines as antiparasitic agents,[8] two of which, trifluralin (**1**)[9−13] and chloralin (**2**),[9] have been reported to be effective against *Leishmania*. Trifluralin is a commercial herbicide used in the United States since the 1960s.[14] Chloralin, the industrial precursor to trifluralin, has been reported to be 100 times more potent than trifluralin against *Leishmania* promastigotes.[9] The same investigators reported that trifluralin's activity is due solely to the chloralin impurity present in commercial trifluralin preparations and postulated that the molecular mechanism for activity is the inhibition of microtubule formation.



1 Trifluralin



2 Chloralin

Tubulin assembles to form microtubules, which play critical roles in chromosome segregation, organelle transport, and cell structure maintenance. It has previously been suggested that the C-4 chloro moiety of chloralin is displaced by one or more of the 25 cysteine residues present in leishmanial tubulin to form a tubulin−deschlorochloralin complex thereby preventing microtubule assembly.[9] Recently, it has been shown that chloralin interferes with microtubule assembly in vitro, while trifluralin does not.[15] Similar effects on mammalian tubulin have also been described with the small aromatic electrophiles 1-fluoro-2,4-dinitrobenzene[16] and 2,4-dichlorobenzyl thiocyanate.[17]

The presence of nitro moieties in a chemotherapeutic agent, such as chloralin, presents the potential for carcinogenicity.[18] We have therefore embarked upon the syntheses of chloralin analogues that have substituted an electron-withdrawing sulfonamido functionality in lieu of the nitro moieties in hopes of discovering a chemotherapeutic agent that retains chloralin's activ-

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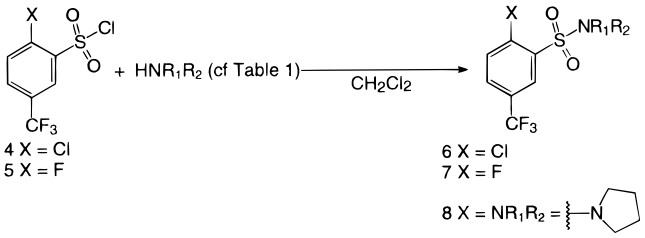
Scheme 1. Reaction Sequence for Sulfonamide Formation



ity without its corresponding potential for toxicity. This manuscript reports the results of that endeavor.

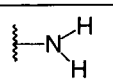
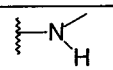
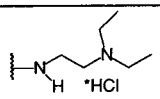
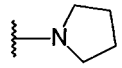
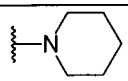
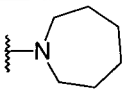
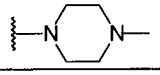
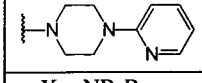
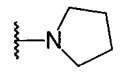
Results and Discussion

Synthetic Discussion. Recent structure−activity relationship analysis of chloralin has revealed that the C-4 chloride moiety as well one *o*-nitro functionality are necessary for activity.[9] It is therefore hypothesized that a bioisostere of the nitro moiety, the sulfonamido group, should retain the necessary electronic features contributing to chloralin's activity without the corresponding toxicity (or potential carcinogenicity) inherent to the nitro moiety. Thus, eight different amines were reacted with chloro sulfonyl chloride **4** in the addition−displacement reaction, depicted in Scheme 1, to give compounds **6a**−**h**. The amines varied from simple ammonia to medium sized cyclic amines such as pyrrolidine and hexamethyleneimine. The corresponding C-4 fluoro analogues **7a**−**h** were similarly synthesized from fluoro sulfonyl chloride **5** in order to determine the steric and electronic requirements at position 4. Bipyrrolidyl-substituted sulfonamide **8** was specifically generated after being detected as a minor side product in the pyrrolidyl addition−displacement reaction.

Initial experiments utilized a weak base (potassium carbonate or triethylamine) and were conducted at room temperature. These reactions provided the insight that the weak bases neither assisted nor hindered the reaction sequence. It was also noted that the attacking amine displaced the C-4 halogen if ample reaction time existed. Therefore, subsequent reactions excluded the use of either weak base, were conducted at 0 °C, and were shortened to 5 min or less. Yields ranged from moderate (51%) in the initial trials to excellent (91%) in the latter trials.

Biological Discussion. The 17 potential chemotherapeutics were evaluated in vitro against amastigote-like *Leishmania donovani* parasites (cf. Table 1), and two (**7f**, **8**) were further evaluated against *L. donovani* amastigotes in a hamster model (cf. Table 2). The in vitro evaluations used chloralin and Pentostam as standards, while the standards for the hamster model were Glucantime and chloralin. The in vitro IC_{50} value for chloralin was determined to be 1.3 ± 0.1 μM against the *L. donovani* parasites, while Pentostam had an IC_{50} value of 329 ± 8 μM (based on antimony content). Any synthesized analogue whose in vitro IC_{50} value exceeded

Table 1. Sulfonamide Activity and Log *P* Values

Amine Derivative (NR_1R_2)	Compound Number		IC_{50}±Standard Error (μM)[a]		Log P	
	6 X =Cl	7 X = F	6 X =Cl	7 X = F	6 X =Cl	7 X = F
	6a	7a	IA	IA	1.98	1.68
	6b	7b	IA	IA	2.63	2.08
	6c	7c	IA	IA	3.85	3.30
	6d	7d	115±25	IA	3.44	2.90
	6e	7e	110±21	418±193	4.01	3.47
	6f	7f	56±9	108±9	4.57	4.03
	6g	7g	321±29	199±37	3.16	2.61
	6h	7h	44±5	IA	3.45	2.91
$X = NR_1R_2 =$ 	8		23±12		3.57	
chloralin	2		1.3±0.1		3.43	
pentostam	standard		329±8		N/A	

[a] IA, the compound's IC_{50} value exceeded 450 μM.

Table 2. In Vivo Test Results against Visceral *L. donovani* in Hamsters

compound	dosage level (mg/kg)	% suppression of parasitemia
glucantime	52	27
	208	73
chloralin	52	21
	208	32
7f	13	11
	52	13
	208	19
8	13	16
	52	29
	208	30

450 μM was designated inactive. The data indicate that, as a group, the C-4 chloro analogues had greater activity than the corresponding C-4 fluoro compounds, with only one exception, analogue **7g**. Both sets of amino (**6a, 7a**) and methylamino (**6b, 7b**) analogues displayed inactivity. The two diethylenediamine compounds (**6c, 7c**) were also inactive. Analogues which incorporated the sulfonamido nitrogen into a five (**6d**, **7d**), six (**6e**, **7e**), or seven (**6f**, **7f**) membered heterocyclic ring had better activity. Of these six compounds, analogues **6f** and **7f** demonstrated the best inhibition (**6f**, $IC_{50} = 56 \pm 9$ μM; **7f**, $IC_{50} = 108 \pm 9$ μM).

The *N*-methylpiperazyl (**6g**, **7g**) and 2-pyridylpiperazyl (**6h**, **7h**) derivatives demonstrated moderate to good activity. The C-4 fluoro *N*-methylpiperazyl analogue (**7g**) had activity in the 200 μM range, while the C-4 chloro 2-pyridylpiperazyl analogue (**6h**) displayed the lowest IC_{50} value (44 ± 5 μM) of the halogen C-4-substituted analogues. Dipyrrolidine analogue (**8**) exhibited the most potency against the *L. donovani* parasites ($IC_{50} = 23 \pm 12$ μM).

The partition coefficient (log *P*) for each analogue, including chloralin,[19] was calculated and compared with each analogue's IC_{50} value in hopes of finding good correlation between activity and log *P* values. Unfortunately, no correlation could be extrapolated between these two properties.

The dipyrrolidyl (**8**) and the 4-fluoro hexamethyleneimine (**7f**) analogues were evaluated against the Khartoum strain of *L. donovani* in a hamster model,[20] using chloralin and Glucantime as standards. The animals, six per group, were injected intracardially with 1.0×10^7 amastigotes obtained from spleens of donor hamsters. Analogues **7f** and **8**, as well as the standards, were introduced into the hamsters by intramuscular injection on day 3 after infection and screened 'blind' at the indicated dosages (Table 2). The therapeutics were administered for 4 consecutive days, and on day 7 after infection, the animals were sacrificed and the total parasite number per liver was determined. Neither chloralin nor either analogue suppressed the *L. donovani* parasites in sufficient quantities at the indicated dosage levels to be considered active in this evaluation.

Conclusions

Nine analogues displayed in vitro activity against the *L. donovani* parasite ($IC_{50} < 450$ μM). Their efficacies varied widely with the most promising candidate, analogue **8**, exhibiting an IC_{50} value of 23 ± 12 μM. This result is an order of magnitude lower than that of the current therapeutic, Pentostam ($IC_{50} = 329 \pm 8$ μM antimony), and is an order of magnitude higher than the IC_{50} value obtained for chloralin ($IC_{50} = 1.3 \pm 0.1$ μM). Therefore, analogue **8** could be considered a lead compound for further development, provided, of course, that it is nontoxic and displays in vivo activity.

The steric and electronic requirements at position C-4 were also explored. It was originally believed that the C-4 fluoro derivatives would exhibit greater activity than the corresponding C-4 chloro derivatives because the fluoro moiety would impart less steric hindrance at the C-4 displacement site and would also impart greater electronegativity on the entire molecule thereby increasing antiparasitic activity. The biological data proved otherwise: the C-4 chloro substituents exhibited lower IC_{50} in vitro values and hence greater therapeutic potency than the C-4 fluoro analogues.

Finally, dipyrrolidyl analogue **8** and fluoro hexamethyleneimine analogue **7f** were evaluated in vivo. Neither of these two compounds nor chloralin displayed activity against visceral *L. donovani* parasite in the hamster model. This could be attributed to the lability of the C-4 substituents. It is possible that an undetermined nucleophile displaced the C-4 moiety at the injection site. Another possible explanation is this class of compounds simply has poor transportation in mammalian cells. However, the excellent in vitro activity displayed by analogue **8** cannot be readily dismissed.

This analogue represents an entirely new structural class of antileishmanial agents that should be expanded upon and evaluated. Compound **8** might even significantly suppress the *L. donovani* parasite if administered by another route such as intravenously or by gavage. Also, analogue **8** might be active against cutaneous *Leishmania* when administered in ointment form since trifluralin displays activity in that fashion.[21]

Finally, the proposed mechanism of action for this class of compounds might not be microtubule inhibition. Eight analogues (**6a**−**g**, **7e**, **8**) were tested against purified tubulin at 50 μM to determine if microtubule assembly was inhibited. None were found inhibitory (chloralin's $IC_{50} = 22$ μM);[15] therefore the observed in vitro activity is ascribed to an as of yet unknown mechanism of action.

Experimental Section

Parasite Drug Susceptibility Assay. 1. General: The *Leishmania donovani* parasites (WHO designation: MHOM/SD/62/1S-CL2D) were maintained as axenic amastigote-like forms by serial passage at 37 °C in a humid atmosphere containing 5% CO_2 using a slightly modified version of a known medium.[22]

2. Drug Assay: *L. donovani* amastigote-like forms were seeded at 10^6 cells/mL in 96-well flat-bottom plates (Costar) in the amastigote medium described earlier in the presence or absence of drug. The maximum concentration of DMSO in each well was 1.25% (v/v), which had no effect on the growth of the parasites. Plates were incubated at 37 °C in a humid 5% CO_2 atmosphere for 72 h; then 12 μL of the aqueous Cell Titer solution (Promega) was added to each well according to the instructions of the manufacturer. The Cell Titer solution contains a compound that is reduced by cellular dehydrogenases to give a product that is measured spectrophotometrically. Plates were returned to the 37 °C incubator for a further 8−12 h, and then the absorbance of each well was measured at 490 nm using a Dynatech MR 5000 plate reader. IC_{50} values for each of the drugs were determined with the aid of the program TableCurve 2D, version 3 (Jandel Scientific). The

log dose−response equation $y = a + b/(1 + (x/c)^d)$ was used to calculate IC_{50} values, where x is drug concentration, y is absorbance at 490 nm, a is lower asymptote, b is the difference between the upper and lower asymptote, c is IC_{50}, and d is slope.

General Chemical Procedures. 2-Fluoro-5-(trifluoromethyl)benzenesulfonyl chloride and 2-chloro-5-(trifluoromethyl)benzenesulfonyl chloride were obtained under contract from Ash-Stevens Inc., Detroit, MI. Melting points were determined using a Thomas-Hoover capillary apparatus and are reported uncorrected. ^{1}H NMR spectra were recorded on a Bruker AC-300 spectrometer at 300 K using tetramethylsilane as an internal standard and are reported in parts per million. All infared spectra were obtained using a Nicolet 20SXB FTIR spectrometer and were recorded in wavenumbers (cm^{-1}). Mass spectra were obtained using a Hewlett-Packard 5970 series mass selective detector. Microanalyses were conducted by Atlantic Microlabs (Norcross, GA) and were within ±0.40% for elements indicated. Silica gel column chromatography was carried out using Merck grade 9385 (230−400 mesh, 60 Å) silica gel. Thin-layer chromatography was performed on Analtech Uniplates HPTLC-HLF normal phase silica gel plates with organic binder and indicated solvents.

General Method for Sulfonamide Formation (6a−h, 7a−h, 8). 2-Fluoro-5-(trifluoromethyl)benzenesulfonyl chloride or 2-chloro-5-(trifluoromethyl)benzenesulfonyl chloride was dissolved in methylene chloride and brought to 0 °C. The corresponding amine was added neat. After approximately 5−15 min (reaction times varied) the reactions were diluted with water, transferred to a separatory funnel, and washed with hydrochloric acid (1 M), aqueous sodium carbonate (10%), and water. The combined organic layers were concentrated in vacuo and subjected to flash chromatography (using indicated TLC solvents) to yield crystalline compounds (except where no melting point is given).

2-Chloro-5-(trifluoromethyl)benzenesulfonamide (6a): yield 92%; R_f = 0.51 (9:1 $CHCl_3$−$(CH_3)_2CO$); mp 158.5−160 °C; IR (smear) 3396, 3284, 1606, 1575 cm^{-1}; ^{1}H NMR (acetone-d_6) δ 8.31 (s, 1H), 7.99 (dd, 1H, J = 8.4, 1.8 Hz), 7.90 (d, 1H, J = 8.4 Hz), 7.05 (s, N−H), 2.79 (s, N−H); MS m/e 259 (M^+), 243, 196, 179. Anal. ($C_7H_5ClF_3NO_2S$) C, H, N, Cl, S.

2-Fluoro-5-(trifluoromethyl)benzenesulfonamide (7a): yield 97%; R_f = 0.37 (9:1 $CHCl_3$−$(CH_3)_2CO$); mp 125−127 °C; IR (KBr) 3384, 3280, 3131, 3085, 1617 cm^{-1}; ^{1}H NMR (acetone-d_6) δ 8.15 (dd, 1H, J = 6.3, 1.2 Hz), 8.08 (m, 1H), 7.63 (t, 1H, J = 9.1 Hz), 7.11 (s, N−H), 2.80 (s, N−H); MS m/e 243 (M^+), 227, 179, 163. Anal. ($C_7H_5F_4NO_2S$) C, H, N, S.

***N*-Methyl-2-chloro-5-(trifluoromethyl)benzenesulfonamide (6b):** yield 82%; R_f = 0.27 (4:1 hexane−EtOAc); mp 97.5−99 °C; IR (smear) 3319, 3106, 1607, 1575 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.37 (s, 1H), 7.78 (d, 1H, J = 8.3 Hz), 7.68 (d, 1H, J = 8.3 Hz), 5.04 (s, N−H), 2.69 (d, 3H, J = 5.3 Hz); MS m/e 273 (M^+), 254, 243, 209, 179. Anal. ($C_8H_7ClF_3NO_2S$) C, H, N, Cl, S.

***N*-Methyl-2-fluoro-5-(trifluoromethyl)benzenesulfonamide (7b):** yield 75%; R_f = 0.28 (4:1 hexane−EtOAc); mp 88−89 °C; IR (KBr) 3276, 3119, 1614, 1495 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.20 (d, 1H, J = 5.9 Hz), 7.86 (m, 1H), 7.63 (t, 1H, J = 9.0 Hz), 4.75 (s, N−H), 2.76 (d, 3H, J = 5.2 Hz); MS m/e 257 (M^+), 248, 227, 163. Anal. ($C_8H_7F_4NO_2S$) C, H, N, S.

***N*,*N*-Diethylenediamino-2-chloro-5-(trifluoromethyl)benzenesulfonamide (6c):** yield 94%; R_f = 0.38 (MeOH, HCl salt); mp (HCl) 147−149 °C; IR (neat) 3309, 3080, 2972, 2821, 1605 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.37 (s, 1H), 7.75 (dd, 1H, J = 8.3, 1.5 Hz), 7.66 (d, 1H, J = 8.3 Hz), 2.96 (t, 2H, J = 5.6 Hz), 2.52 (t, 2H, J = 5.6 Hz), 2.44 (q, 4H, J = 7.1 Hz), 0.96 (t, 6H, J = 7.1 Hz); MS m/e 357 (M^+ − 1), 341, 286, 243, 179. Anal. (HCl salt) ($C_{13}H_{19}Cl_2F_4N_2O_2S$) C, H, Cl, N, S.

***N*,*N*-Diethylenediamino-2-fluoro-5-(trifluoromethyl)benzenesulfonamide (7c):** yield 36%; R_f = 0.38 (MeOH, HCl salt); mp (HCl) 140−141 °C; IR (smear) 3300, 3079, 2974, 2823, 1612, 1499 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.21 (dd, 1H, J = 6.3, 1.7 Hz), 7.84 (m, 1H), 7.35 (t, 1H, J = 8.9 Hz), 3.03 (t, 2H, J = 5.9 Hz), 2.53 (t, 2H, J = 5.9 Hz), 2.43 (q, 4H, J = 7.1 Hz), 0.96 (t, 6H, J = 7.1 Hz); MS m/e 323 (M^+ − 19), 270, 227, 163. Anal. (HCl salt) ($C_{13}H_{19}ClF_4N_2O_2S$) C, H, Cl, N, S.

Pyrrolidyl-2-chloro-5-(trifluoromethyl)benzenesulfonamide (6d): yield 90%; R_f = 0.19 (9:1 hexane−EtOAc); mp 89−91 °C; IR (smear) 3103, 2983, 2883, 1604 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.36 (s, 1H), 7.73 (d, 1H, J = 8.4 Hz), 7.65 (d, 1H, J = 8.4 Hz), 3.44 (m, 4H), 1.93 (m, 4H); MS m/e 312 (M^+ − 1), 243, 179, 70. Anal. ($C_{11}H_{11}ClF_3NO_2S$) C, H, Cl, N, S.

Pyrrolidyl-2-fluoro-5-(trifluoromethyl)benzenesulfonamide (7d): yield 71%; R_f = 0.20 (9:1 hexane−EtOAc); mp 71.5−72.5 °C; IR (smear) 3315, 3053, 2987, 2882, 1597 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.21 (dd, 1H, J = 6.0, 2.0 Hz), 7.83 (m, 1H), 7.34 (t, 1H, J = 9.0 Hz), 3.40 (m, 4H), 1.89 (m, 4H); MS m/e 296 (M^+ − 1), 278, 227, 163. Anal. ($C_{11}H_{11}F_4NO_2S$) C, H, N, S.

Piperadyl-2-chloro-5-(trifluoromethyl)benzenesulfonamide (6e): yield 64%; R_f = 0.43 (9:1 hexane−EtOAc); mp 86.5−88 °C; IR (smear) 3100, 2943, 2859, 1606 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.32 (s, 1H), 7.72 (dd, 1H, J = 8.3, 1.8 Hz), 7.65 (d, 1H, J = 8.3 Hz), 3.30 (m, 4H), 1.61 (m, 6H); MS m/e 326 (M^+ − 1), 308, 286, 243, 179. Anal. ($C_{12}H_{13}ClF_3NO_2S$) C, H, Cl, N, S.

Piperadyl-2-fluoro-5-(trifluoromethyl)benzenesulfonamide (7e): yield 95%; R_f = 0.15 (19:1 hexane−EtOAc); mp 84.5−85.5 °C; IR (smear) 3081, 2949, 2866, 1613, 1501 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.14 (dd, 1H, J = 5.9, 1.8 Hz), 7.84 (m, 1H), 7.36 (t, 1H, J = 9.0 Hz), 3.21 (m, 4H), 1.66 (m, 4H), 1.53 (m, 2H); MS m/e 310 (M^+ − 1), 270, 227, 179, 163. Anal. ($C_{12}H_{13}F_4NO_2S$) C, H, N, S.

Hexamethyleneimino-2-chloro-5-(trifluoromethyl)benzenesulfonamide (6f): yield 86%; R_f = 0.31 (9:1 hexane−EtOAc); mp 53−55 °C; IR (smear) 3100, 2933, 2860, 1605 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.35 (s, 1H), 7.72 (d, 1H, J = 8.3 Hz), 7.65 (d, 1H, J = 8.3 Hz), 3.40 (t, 4H, J = 5.6 Hz), 1.67 (m, 8H); MS m/e 341 (M^+), 322, 286, 243, 179. Anal. ($C_{13}H_{15}ClF_3NO_2S$) C, H, Cl, N, S.

Hexamethyleneimino-2-fluoro-5-(trifluoromethyl)benzenesulfonamide (7f): yield 73%; R_f = 0.30 (7:3 hexane−$CHCl_3$); mp 75−76 °C; IR (smear) 3077, 2931, 2858, 1612, 1601 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.19 (dd, 1H, J = 6.1, 1.7 Hz), 7.81 (m, 1H), 7.32 (t, 1H, J = 9.0 Hz), 3.38 (m, 4H), 1.65 (m, 8H); MS m/e 325 (M^+), 306, 270, 227, 163. Anal. ($C_{13}H_{15}F_4NO_2S$) C, H, N, S.

***N*-Methylpiperazyl-2-chloro-5-(trifluoromethyl)benzenesulfonamide (6g):** yield 87%; R_f = 0.33 (19:1 EtOAc−MeOH); mp 64−66 °C; IR (neat) 3100, 3079, 2943, 2852, 2800, 1606 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.31 (s, 1H), 7.73 (dd, 1H, J = 8.3, 1.9 Hz), 7.66 (d, 1H, J = 8.3 Hz), 3.36 (t, 2H, J = 5.0 Hz), 2.46 (t, 2H, J = 5.0 Hz), 2.30 (s, 3H); MS m/e 342 (M^+), 323, 179, 144. Anal. ($C_{12}H_{14}ClF_3N_2O_2S$) C, H, Cl, N, S.

***N*-methylpiperazyl-2-fluoro-5-(trifluoromethyl)benzenesulfonamide (7g):** yield 59%; R_f = 0.34 (9:1 EtOAc−hexane); mp 90.5−92 °C; IR (smear) 2943, 2855, 1612, 1499 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.12 (dd, 1H, J = 4.1, 1.9 Hz), 7.84 (m, 1H), 7.35 (t, 1H, J = 9.0 Hz), 3.26 (m, 2H), 2.49 (m, 2H), 2.30 (s, 3H); MS m/e 326 (M^+), 307, 227, 163. Anal. ($C_{12}H_{14}F_4N_2O_2S$) C, H, N, S.

***N*-(2-Pyridyl)piperadyl-2-chloro-5-(trifluoromethyl)benzenesulfonamide (6h):** yield 91%; R_f = 0.28 (4:1 hexane−EtOAc); mp 50.5−52.5 °C; IR (smear) 3099, 3006, 2919, 2858, 1604 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.34 (s, 1H), 8.18 (dd, 1H, J = 4.8, 3.6 Hz), 7.74 (dd, 1H, J = 8.3, 1.6 Hz), 7.66 (d, 1H, J = 8.3 Hz), 7.49 (td, 1H, J = 8.7, 1.8 Hz), 6.65 (m, 2H), 3.64 (m, 2H), 3.44 (m, 2H); MS m/e 405 (M^+), 207, 179, 162. Anal. ($C_{16}H_{15}ClF_3N_3O_2S$) C, H, Cl, N, S.

***N*-(2-Pyridyl)piperadyl-2-fluoro-5-(trifluoromethyl)benzenesulfonamide (7h):** yield 66%; R_f = 0.30 (4:1 hexane−EtOAc); mp 125.5−126.1 °C; IR (smear) 3051, 3008, 2984, 2823, 1610 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.16 (m, 1H), 7.85 (m, 1H), 7.49 (td, 1H, J = 7.4, 1.8 Hz), 7.35 (t, 1H, J = 9.0 Hz), 6.65 (m, 2H), 3.67 (t, 2H, J = 4.8 Hz), 3.35 (t, 2H, J = 4.8 Hz); MS m/e 389 (M^+), 370, 227, 162. Anal. ($C_{16}H_{15}F_4N_3O_2S$) C, H, N, S.

Pyrrolidyl-2-pyrrolidyl-5-(trifluoromethyl)benzenesulfonamide (8): yield 90%; R_f = 0.38 ($CHCl_3$); mp 89−91 °C; IR (smear) 2973, 2876, 1614, 1547 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.77 (d, 1H, J = 1.2 Hz), 7.49 (dd, 1H, J = 8.9, 2.0 Hz), 6.95 (d, 1H, J = 8.9 Hz), 3.61 (t, 4H, J = 6.6 Hz), 3.42 (t, 4H, J = 6.6 Hz), 1.98 (m, 8H); MS *m/e* 348 (M^+), 329, 278, 248, 213. Anal. ($C_{15}H_{19}F_3N_2O_2S$) C, H, N, S.

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